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(21) International Application Number: PCT/GB92/00551 (22) International Filing Date: 25 March 1992 (25.03.92) (30) Priority data: 9108080.4 15 April 1991 (15.04.91) GB (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : LEA, Philip [GB/GB]; COKE, Mark [GB/GB]; MORWOOD, Kim [GB/GB]; SMITH, Andrew, William [GB/GB]; SmithKline Beecham Consumer Brands Research Centre, St. George's Avenue, Weybridge, Surrey KT13 0DE (GB).		(74) Agents: WHITE, Susan, Mary et al.; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GF (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US. Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF GASTRITIS (57) Abstract A pharmaceutical composition for use in the treatment of gastric disorders associated with <i>Helicobacter pylori</i> comprising an antimicrobial agent optionally co-administered with a release-delaying substance.		

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PHARMACEUTICAL COMPOSITION FOR THE TREATMENT
OF GASTRITIS

The present invention relates to pharmaceutical compositions of antimicrobial agents active against Helicobacter pylori and their use in the treatment of gastrointestinal disorders associated with Helicobacter pylori infection.

Helicobacter pylori (formerly known as Campylobacter pyloridis) is a spiral-shaped Gram-negative organism which appears to live beneath the mucus layer of the stomach. Many recent studies have shown an association between the presence of H. pylori in the gastric mucosa and histologically confirmed gastritis.

In the light of these results, it has been suggested that the organism may be a pathogen which causes, or at least exacerbates, gastritis, and may also be important in the aetiology of peptic ulceration. Reviews on the state of the art include those by C.A.M. McNulty in J. Infection, 1986, 13, 107-113, and by C.S. Goodwin et al. in J. Clin. Pathol., 1986, 39, 353-365.

H. pylori is known to be susceptible to a large number of antimicrobial agents *in vitro*. Furthermore, several workers have shown that treatment of gastritis with antimicrobial agents, for example β -lactam antibiotics such as amoxycillin, or bismuth salts, leads to eradication of the associated H. pylori organisms *in vivo*.

GB 2 243 549 A (Reckitt & Colman), published November 6, 1991, claims the use of the non-antibiotic antimicrobial agent triclosan for the preparation of a medicament for the treatment of gastrointestinal disorders associated with Helicobacter pylori infection. According to GB 2 243 549 A, the medicament may be formulated as a gastric sustained release composition having prolonged residence time within the stomach and continuously releasing triclosan during that time. Triclosan compositions formulated so as to produce floating alginate rafts within the stomach, or as muco-adherent coated granules or spheroids, are identified as suitable sustained release compositions.

GB 2 243 549 A further describes, for tablets, a co-formulation and, for tablet or liquid presentations, co-administration with a pharmaceutically acceptable

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solid carboxylic acid, or salt thereof, in order to overcome the tendency for elevated stomach pH, observed with certain patients suffering from Helicobacter pylori infections, to reduce the ability for alginate rafts to float. Citric acid is referred to as a suitable acid for this purpose.

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For comparative purposes, GB 2 243 549 A discloses the *in vitro* testing of 11 antimicrobial compounds in addition to triclosan versus Helicobacter pylori, based on methods described by McNulty et al. (Antimicrobial Agents & Chemotherapy, 28, 837-838, 1985). MIC results for triclosan, tinidazole, 10 cetalkonium chloride, cetyl pyridinium chloride, clioquinol, hexetidine, dichlorophen, halquinol, 4-hexyl recorcinol, hibitane (chlorhexidine gluconate), PCMX (chorloxylenol), and guaiacol are disclosed.

J. Pediatr. Gastroenterol. Nutr., 9(1), 46-8, (1989), describes Helicobacter 15 pylori as being extremely sensitive to the anti-infective activity of benzocaine, a commonly used topical anaesthetic.

It has now been found that activity against Helicobacter pylori is also conferred by a range of readily available substances, in particular substances 20 which already have utility as antimicrobial agents.

Included within this range of substances are groups of antimicrobial agents respectively defined as cationic antimicrobial agents, benzene derivatives, phenols, and amines, and certain naturally occurring substances, for example 25 certain plant extracts.

Included within the group known as cationic antimicrobial agents are pyridinium and isoquinolinium compounds, guanides, for example bis-biguanides, and a range of quaternary ammonium salts. A number of cationic 30 antimicrobial agents have shown activity against human oral bacteria which has promoted their use in the treatment or prophylaxis of periodontal diseases and dental caries.

Examples of substances which have now been found to have *in vitro* activity 35 against strains of Helicobacter pylori resident in the gastric and duodenal mucosa, and hence to have potential utility for the *in vivo* treatment of gastric disorders associated with Helicobacter pylori, include benzene derivatives such as benzoic acid, benzyl alcohol, dibromopropamide

isethionate, 2,4-dichlorobenzyl alcohol, and hydroxy benzoates including methy-, ethyl-, propyl-, n-butyl-, n-heptyl- and benzyl-p-hydroxy benzoates; phenols such as amylmetacresol, chlorochresol, phenol, trichlorophenol and creosote; amines such as hexamine; bis-biguanides such as chlorhexidine
5 hydrochloride; quaternary ammonium compounds such as benzalkonium chloride, dequinium chloride, domiphen bromide and cetrimide; pyrimidines such as hexetidine citrate; glycerol esters such as glycerol monolaurate; dyclonine hydrochloride; miconazole; mupirocin; polynoxylin; povidone iodine; sorbate; and natural products such as garlic and tea tree oil.

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Accordingly, the present invention provides the use of these substances hereinbefore identified in the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori.

15 It has been found that treatment of H.pylori associated gastritis with antimicrobial agents given by a conventional oral dosing regimen may require a prolonged course of therapy to be effective. Furthermore, follow-up of patients cleared of H.pylori infection by antimicrobial treatment has shown that relapse (rather than reinfection) can be a problem.

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In another aspect of the invention, substances having activity against H. pylori may be formulated as gastric controlled release compositions, more especially as compositions which prolong residence time of the antimicrobial agent within the stomach.

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Bioadhesive materials have received considerable attention as platforms for controlled drug delivery. They can be targeted to specific drug administration sites, prolong the residence time and ensure an optimal contact with the absorbing surface. Many different types of bioadhesive
30 materials, both natural and synthetic, can be used in the design of controlled drug delivery systems.

Sucralfate, a basic aluminium sulphate sucrose complex, is an ulcer-preventing agent having anti-pepsin and antacid properties. It has
35 muco-adherent properties such that when administered orally it reacts with gastric juice to form a sticky paste which protects the mucosa by coating, and also binds to ulcer-affected sites. The preparation and use of sucralfate is described in for example US patent No.3432489 and "The Merck Index" 11th

edition (1989) p1400 entry No 8853.

- EP-A-0 403 048 (Warner-Lambert) describes medicated compositions comprising sucralfate and a therapeutically effective amount of a medicament which is, a) substantially water insoluble, or b) a mixture of a water-soluble medicament and a release-delaying material which on admixture forms a substantially water-insoluble medicament. The *in-vitro* testing of a sucralfate/benzoic acid composition against Escherichia coli is described.
- 10 US 4,615 697 (Robinson et al.) discloses a controlled release composition comprising an effective amount of a treating agent, which may be a medicament, and a bioadhesive material which is a water-swellaable and water-insoluble, fibrous, cross-linked carboxy-functional polymer. The controlled release compositions are described as adhering to the skin or the mucous membranes in the presence of water.

Accordingly, in this further aspect, the present invention relies on the combination or co-administration of an antimicrobial agent which is active against H. pylori selected from the group consisting of cationic antimicrobial agents, for example benzene derivatives such as benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamide isethionate, 2,4-dichlorobenzyl alcohol, and hydroxy benzoates including methyl-, ethyl-, propyl-, n-butyl-, n-heptyl- and benzyl-p-hydroxy benzoates; phenols such as amylmetacresol, chlorochresol, chloroxyleneol, clioquinol, phenol, trichlorophenol and creosote; amines such as hexamine; bis-biguanides such as chlorhexidine gluconate and chlorhexidine hydrochloride; quaternary ammonium compounds such as benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequilibrium chloride, domiphen bromide and cetrimide; pyrimidines such as hexetidine and hexetidine citrate; glycerol esters such as glycerol monolaurate; dyclonine hydrochloride; miconazole; mupirocin; polynoxylin; povidone iodine; sorbate; and natural products such as garlic and tea tree oil, with one or more substances providing a sustained release and/or prolonged retention of the antimicrobial agent in the stomach, so as to overcome, or at least mitigate, the disadvantages associated with conventionally formulated antimicrobial agents and provide an effective treatment for H. pylori infections of the gastric and duodenal mucosa in humans and domestic animals.

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In this further aspect, the present invention also provides a pharmaceutical composition comprising one or more such antimicrobial agents effective against H.pylori organisms, and one or more substances providing a sustained release and/or prolonged retention of the antimicrobial agent in the stomach.

The present invention extends to these compositions for use in therapy and to the use of these compositions in the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori.

The antimicrobial agent may for example be co-formulated, suitably by intimate admixture, with a muco-adherent or bioadhesive substance to form a bioadhesive complex. Such a complex confers the additional benefit of locally targetting the antimicrobial agent to the mucus layer of the stomach wall.

Bioadhesive materials suitable for use in compositions of the present invention include materials, both natural and synthetic, which are capable of adhering to biological surfaces such as mucus membranes. Examples of bioadhesive materials include natural gums and plant extracts and synthetic materials such as sucralfate, cellulose derivatives, acrylic acid and methacrylic acid derivatives, for example cross-linked acrylic and methacrylic acid copolymers available under the Trade Names CARBOPOL and POLYCARBOPHIL.

Antimicrobial agents effective against H.pylori may alternatively be formulated to produce a floating alginate raft within the stomach. Such formulations may include solid and liquid dosage forms, and may be prepared according to processes known to persons skilled in the art, for example as described in GB 2 243 549 A.

Controlled release dosage forms, for example beadlets or granules, optionally encapsulated or compressed to form tablets, also form part of the invention. Advantageously, beadlets or granules are coated, layered, or form an intimate, homogeneous matrix with release-delaying materials. Such dosage forms may be prepared using conventional techniques known in the art.

The composition of the invention may be made up in the form of a swallow tablet, a chewable tablet or a water dispersible tablet. Alternatively it may

be supplied as a water-dispersible powder, either for dispersion immediately prior to administration or for dispensing in liquid form, as a suspension or as a liquid emulsion. Suitable water-dispersible formulations include soluble effervescent or non-effervescent powders.

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The compositions of the present invention may also contain appropriate additives, for example preservatives, buffering agents, suspending agents, flavourings, bulking agents, binders, adhesives, lubricants, disintegrants, colouring agents, sweeteners, adsorbents, thickeners, suspending agents, and
10 diluents including water, appropriate to their form.

If desired, the release of the antimicrobial agent may be altered by changing its particle size, or by applying a suitable coating particularly to tablet forms. Coatings able to retard the release of pharmaceuticals are well known in the
15 art of pharmaceutical formulation, and include polymers such as acrylic resins (for example the material sold by Rohm Pharma under the trade name 'Eudragit') and cellulose esters (for example ethyl cellulose).

An encapsulated or delayed release formulation according to the invention
20 may be any such form well known in the art. Suitable coating materials include water-based coatings, solvent-based coatings and colloidal dispersions. Lipids may also be used to form liposome-type formulations.

Preferred antimicrobial agents for use in the treatment of gastrointestinal
25 disorders associated with H. pylori are cationic antimicrobial agents, in particular hexetidine and hexetidine citrate, chlorhexidine gluconate and chlorhexidine hydrochloride, benzalkonium chloride, dequelinium chloride, cetyl pyridinium chloride, cetrimide, and domiphen bromide.

30 The antimicrobial agent is present in compositions of the invention in an appropriate amount to provide an effective dose, which will depend on the pharmacological properties of the compound employed. Normally a single dose used to treat an adult human will provide from 0.01mg to 100mg, generally 0.1 to 15mg of antimicrobial agent.

35

For example, a suitable single dose of chlorhexidine hydrochloride lies in the range of 0.1 to 100 mg, typically 1.0 to 15mg. A suitable single dose for cetylpyridinium chloride lies in the range 0.01 to 100 mg, typically 0.1 to

10mg.

For compositions containing sucralfate as muco adherent, a suitable single dose lies in the range 0.5 to 20g, typically 1.0 to 8.0g.

5

The compositions of the present invention may also include additional therapeutic agents useful in the treatment of peptic ulcers and gastritis, and agents which delay gastric emptying, for example methylcellulose, guar gum, fats such as triglyceride esters, and triethanolamine myristate.

10

Compositions of the invention may be administered as often as a physician directs, having regard to the severity of the H.pylori infection. Normally, it is recommended to take a dose two or three times daily, advantageously after meals.

15

Surprisingly, it has also been found that the activity of the antimicrobial agents hereinbefore identified against Helicobacter pylori may be enhanced if these agents are administered in combination with various materials which are not recognised as antimicrobial agents per se, for example chelating agents, surfactants and mixtures thereof.

20

Accordingly, antimicrobial agents and compositions containing antimicrobial agents as hereinbefore described for use in the treatment of Helicobacter pylori, further comprising a chelating agent, a surfactant or mixtures thereof also form part of the invention.

25

Suitable chelating agents include alkyldiamine tetraacetates, for example ethylenediaminetetraacetic acid (EDTA), CaEDTA, and CaNa₂EDTA, EGTA and citrate.

30

Suitable surfactants include ionic and non-ionic surfactants. Examples of non-ionic surfactants include glycerides and the materials commercially available under the Trade Names Tweens and Tritons. Ionic surfactants include fatty acids and quaternary compounds, the anionic surfactant sodium dodecyl sulphate, and amphoteric surfactants such as cocamidopropyl betaine and emulsifiers.

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The compositions of the invention may be prepared by conventional

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pharmaceutical techniques. Thus the composition may, for example, be prepared by mixing together the required ingredients with stirring or grinding to ensure adequate dispersion. Alternatively, some of the ingredients may be mixed together before other ingredients are added.

- 5 Granulation and/or coating techniques may be used at a convenient stage in the process if required.

The invention will now be illustrated by the following examples.

Example 1Activity of Cationic Antimicrobial Agents against Helicobacter Pylori

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The Minimum Inhibitory Concentration (MIC) of representative antimicrobial agents of the invention against human strains of *H. pylori* (*H. pylori* NCTC 11916 & 11637) were assessed using a spiral plater and automatic agar plate pourer, according to the method of Wallace A.S. and Corkill J.E. (J. Microbiol. Methods, 10, 303-310, 1989).
 10 MIC values were calculated according to the equation for the Archimedes spiral.

<u>Compound</u>	<u>MIC Value (mg/l)</u>		<u>Kill Time</u>
	<u>NCTC 11916</u>	<u>NCTC 11637</u>	<u>(mins)</u>
benzalkonium chloride	0.496	0.32	> 30
cetrimide	1.217	1.217	> 30
chlorhexidine HCl	3.33	3.81	> 30
dequilinium chloride	1.217	0.716	< 30
glycerol monolaurate	2.16	1.828	< 30
hexetidine citrate	2.69	2.25	< 5
hexetidine	1.887	1.851	< 1
mupirocin	0.058	0.079	> 30
cetyl pyridinium chloride	0.175	0.168	< 1
domiphen bromide	0.93	0.66	< 30
n-heptyl-p-OH-benzoate	16.5	12.3	< 1
hexyl resorcinol	2.96	2.63	> 30
amylmetacresol	1.49	5.97	

15 Example 2Formulation Examples

- 20 A. A tablet prepared according to standard methods including chlorhexidine hydrochloride (5mg) and sucralfate (1000mg).

- B. A tablet prepared according to standard methods including cetylpyridinium chloride (3mg) and sucralfate (1000mg).
- 5 C. An effervescent powder containing per 5g dose:
- | | | |
|--------------------------|---|------|
| cetyl pridinium chloride | : | 3mg |
| citric acid (anhydrous) | : | 2.2g |
| sodium bicarbonate | : | 2.3g |
| sodium carbonate | : | 0.5g |
- D. An effervescent powder containing per 5g dose:
- | | | |
|-------------------------|---|------|
| domiphen bromide | : | 6mg |
| citric acid (anhydrous) | : | 2.2g |
| sodium bicarbonate | : | 2.3g |
| sodium carbonate | : | 0.5g |
- 10 E. An effervescent powder containing per 5g dose:
- | | | |
|-------------------------|---|------|
| chlorhexidine HCL | : | 5mg |
| citric acid (anhydrous) | : | 2.2g |
| sodium bicarbonate | : | 2.3g |
| sodium carbonate | : | 0.5g |
- 15 F. A tablet containing cetyl pyridinium chloride (3mg) and alginate (1.5g).
(Dosage : 2 tablets t.i.d.)
- G. A tablet containing domiphen bromide (6mg) and alginate (1.5g).
(Dosage : 2 tablets 6.i.d.)
- 20 H. A tablet containing chlorhexidine HCl (5mg) and alginate (1.5g).
(Dosage : 2 tablets t.i.d.)

CLAIMS

1. The use of an antimicrobial agent selected from benzoic acid, benzyl alcohol, dibromopropamide isethionate, 2,4-dichlorobenzyl alcohol, a hydroxy benzoate, amylmetacresol, chlorochresol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine hydrochloride, benzalkonium chloride, dequinium chloride, domiphen bromide, cetrimide, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxilin, povidone iodine, sorbate, garlic and tea tree oil, for the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori.
2. The use of an antimicrobial agent selected from benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamide isethionate, 2,4-dichlorobenzyl alcohol, a hydroxy benzoate, amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine gluconate, chlorhexidine hydrochloride, benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequinium chloride, domiphen bromide, cetrimide, hexetidine, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxilin, povidone iodine, sorbate, garlic and tea tree oil, for the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori, characterised in that the antimicrobial agent is combined with one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach.
3. The use of an antimicrobial agent selected from benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamide isethionate, 2,4-dichlorobenzyl alcohol, a hydroxy benzoate, triclosan, amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine gluconate, chlorhexidine hydrochloride, benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequinium chloride, domiphen bromide, cetrimide, hexetidine, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxilin, povidone iodine, sorbate, garlic and tea tree oil, for the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori, characterised in that the antimicrobial agent is combined with at least one of a chelating agent or a surfactant.

4. A pharmaceutical composition comprising an antimicrobial agent selected from benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamide isethionate, 2,4-dichlorobenzyl alcohol, a hydroxy benzoate, amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine gluconate, chlorhexidine hydrochloride, benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequolinium chloride, domiphen bromide, cetrimide, hexetidine, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxylin, povidone iodine, sorbate, garlic and tea tree oil, and one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach.
5. A pharmaceutical composition as claimed in claim 4 wherein the one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach is a muco-adherent or bioadhesive substance.
6. A pharmaceutical composition as claimed in claim 5 wherein the one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach is a natural gum, a plant extract, sucralfate, a cellulose derivative, or an acrylic acid or methacrylic acid derivative,
7. A pharmaceutical composition as claimed in claim 6 wherein the antimicrobial agent and the muco-adherent or bioadhesive substance are co-formulated as an intimate mixture.
8. A pharmaceutical composition comprising an antimicrobial agent selected from benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamide isethionate, 2,4-dichlorobenzyl alcohol, a hydroxy benzoate, triclosan, amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine gluconate, chlorhexidine hydrochloride, benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequolinium chloride, domiphen bromide, cetrimide, hexetidine, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxylin, povidone iodine, sorbate, garlic and tea tree oil, and at least one of a chelating agent or a surfactant.

9. A pharmaceutical composition as claimed in claim 8 wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA), CaEDTA, and CaNa₂EDTA, EGTA or citrate.
- 5
10. A process for preparing a pharmaceutical composition as claimed in any one of claims 5 to 9 comprising the admixture of the antimicrobial agent with one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach, and/or at least one
- 10 of a chelating agent or a surfactant, and a pharmaceutically acceptable carrier.

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ES	Spain				

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 92/00551

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 A 61 K 31/045 A 61 K 31/05 A 61 K 31/055 A 61 K 31/14 A 61 K 31/155 A 61 K 31/19 A 61 K 31/23 31/235 A 61 K 31/245 31/35 31/415 31/445 31/47 31/505 31/785 31/79		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	FR,M, 2559 (LAB. PHARMACOTECHNIQUE DUBOIS & VINCENT) 1964, see the whole document ---	1-10
Y	FR,M, 677 (R.R. BLAISE) 21 April 1969, see page 1, column 2 ---	1-10
Y	FR,M, 3623 (RHONE-POULENC) 1965, see page 1 ---	1-10
Y	Schweizerische Medizinische Wochenschrift, vol. 118, no. 16, 23rd April 1988, Schwabe & Cie. SA, Bale, CH; J.-O. Gebbers et al.: "Campylobacter pylori: Ursache von Gastritis und Ulkuserkrankheit?", pages 577-583, see page 581 --- -/-	1-3
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
09-07-1992		29. 10. 92
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	Scand. J. Gastroenterol, Suppl. vol. 155, 1988, G.N.J. Tytgat et al.: "Campylobacter pylori", pages 68-81, see page 73 ---	1-3
Y	Acta Gastro-enterologica Belgica, vol. 51, nos. 4-5, July-October 1988, Y. Glupczynski et al.: "Campylobacter pylori-associated gastritis: attempts to eradicate the bacteria by various antibiotics and anti-ulcer regimens", pages 329-337, see page 333 ---	1-3
Y	R. Dolder & F.S. Skinner: Ophthalmika, 3rd Edition, 1983, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, DE; pages 92-94, see page 93 ---	4-10
Y	Journal of Pharmaceutical Sciences, vol. 73, no. 1, January 1984, Am. Pharm. Association, US; G.W. Schieffer et al.: "Simultaneous determination of methyl, ethyl, propyl, and butyl 4-hydroxybenzoates and 4-hydroxybenzoic acid in liquid antacid formulations by gas chromatography", pages 128-131, see page 128 ---	1-10
A	EP,A,0078599 (TEIKOKU CHEMICAL IND. CO.LTD) 11 May 1983, see abstract -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB92/00551

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see form PCT/ISA/206 sent to you 13.08.92.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-10 in part

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9200551
SA 57808

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/10/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-M- 2559		None	
FR-M- 677		None	
FR-M- 3623		None	
EP-A- 0078599	11-05-83	JP-B- 1012267	28-02-89
		JP-C- 1531967	24-11-89
		JP-A- 58038250	05-03-83
		US-A- 4478995	23-10-84

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82